VOL. XXI. September, 1896. No. 9.

THE
Journal
OF
Nervous and Mental Disease

AMERICAN NEUROLOGICAL ASSOCIATION.

Twenty-second Annual Meeting, held in the hall of the College of Physicians of Philadelphia, on June 3, 4, 5, 1896.

(*Continued.*)

EPILEPSY AND OTHER CONVULSIVE DISEASES. A STUDY IN NEURO-DYNAMICS AND PATHOGENESIS.

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ANATOMICAL DIGEST.

THE now well-established doctrine of *the neuron*[1] as the anatomical and physiological unit of the nervous system, with the flood of light recently thrown upon its inter-relations by the epoch making researches of Cajal[2], Golgi[3] and a host of other workers in neuro-histology, prominent amongst whom may be mentioned Berkley[4], [5], and Starr[6], in our own country, has made imperative a recast of our conceptions of neuro-processes in general, and of the anatomico-pathologic basis of certain nervous diseases in particular.

As bearing on these newer *general* conceptions may be cited the contributions of Schafer[7], Broadbent[8], and Gowers[9]; while the more *particular* advances are exemplified in the researches of Hodge[10], Andriezen[11], and Berkley[12].

To sum up the present anatomical status of the subject: The *neuron* (as defined by Waldeyer), comprises the "nerve cell" proper, with all its processes of every kind and their ultimate ramifications. It thus includes the cell, the fibre, the "spongy reticulum" and the "end-organ" of the older terminology. Figure 1 (semi-diagrammatic) represents better than a prolonged description the type of the neuron, as found in the "large pyramidal cell" layer of the cerebral cortex.

The demonstration, by Cajal, of the *individuality of the neuron*, as opposed to the older views of (1) a *recticular continuity* or (2) a *fusion* with an intermediate homogeneous basis substance, must be considered the most important contribution of the century to our knowledge of the structure and functions of the nervous system.

Though anatomically distinct units, neurons are in physiological relation with each other by means of numerous delicate knobs or projections called gemmules or "contact granules," this contact constituting a continuous protoplasmic chain in a functional sense.

So far we may be said to be sailing by the chart, but recently mapped out, it is true, but already traversed sufficiently often to fix our main bearings.

The domain of the unknown however looms up ahead in shadowy outline, and through the fogs of doubt and the mists of uncertainty we may note here and there an apparent landmark. Max Schultze[13], quoted and confirmed by Schafer[7], considers the neuron processes, at least those forming the axis-cylinders of the nerve fibres, as resolvable into bundles of tubules, filled with liquid protoplasm and so accounts for the division of the axis-cylinder at its termination.

If this proposition be true it would seem to the writer to carry with it the bifurcation of the individual tubules at certain places, e. g., opposite the roots of the collateral processes of the axis cylinders; since the outgoing impulses which traverse these tubules must probably be capable of being diverted on occasions; otherwise the motor response to a given sensory income must always be precisely the same, and no provision would exist for "storage" of energy, which must be provided for in any complete scheme of dynamogenesis.

Figure 2 illustrates a portion of such a hypothetical neuron with the tubules of Max Schultze and Schafer, which it will be seen, *traverse* the neuron body ("ganglion cell"). This important fact, which he states is true for some of the tubules at least, gives rise to the equally important conception that the *elaboration of nerve force* takes place in the *processes* themselves and is not the exclusive function of the cell-body as was formerly thought. We will revert to this part of the subject later.

Figure 2 also illustrates the hypothetical bifurcation of the tubules, which has not yet been observed or even looked for so far as the writer is aware. It is quite possible, however, that the tubular appearance noted by Schafer is really due to coagulation of an inter-fibrillary albuminous nutritive fluid.

In this case the problem is much simplified, and we have only to consider the constituents of the ultimate fibrillæ as rows of molecules in constant vibration in all directions, with the rate and intensity of vibration varying according to the intensity of stimuli which influence them; and tending in the direction of least resistance (established by habit). This would allow for a constant moderate "overflow" of "energy currents" at the collaterals, while the main channel of outflow, the axis-cylinder process, would be on account of its direction as well as "habit" the "line of least resistance." Furthermore, structural provision must exist both in the central and peripheral arborizations of the neuron processes, whereby protoplasm may come in contact with protoplasm to complete the physiological chain. This would imply either fenestra in the ultimate tubules toward their terminations,or a total disappearance of the tubular walls. The former view would allow of the projection of the contact granules (gemmules) when in functional activity, and then withdrawal (by amœboid contraction) when at rest. This is in harmony with the hypothesis advanced by Duval[14] and Lepine[15] to account for the sudden appearance and equally prompt disappearance of certain symptoms in hysterical, hypnotic, and other functional states; and also for the suspension of function in large areas of the nervous system during normal sleep.

PHYSIOLOGICAL DIGEST.

As has been already stated, the old view that the neuron body ("nerve cell") is the sole source of nerve energy must probably be abandoned. In its place we have the more tenable doctrine that this cell-body is chiefly, if not entirely, "trophic" in function; subserving the nutritive requirements of the cell-processes, while they in turn are busy with the higher, if not more important duty, of converting various stimuli into nervous activities[9] *. This implies an activity of the neuron-processes which can only be dynamically accounted for on the theory of inter-molecular and inter-atomic motion. It is thus in harmony in a physical sense with any other force. The idea of a "flow" of energy or a nerve "current *per se*" is of course technically untenable in the present state of our knowledge, as it is in physics generally. The term will continue to be used, however, in a conventional sense as the most convenient phraseology, though an entirely erroneous conception originally.

As to the causes that initiate or direct this inter-atomic or inter-molecular motion they can be none other originally than stimuli from without, acting primarily upon the ultimate peripheral arborizations of neurons.

In other words, it is exceedingly probable that nerve elements have no spontaneous or selective activity of their own, but like all protoplasmic bodies they simply possess the power of responding to external influences. Hence even consciousness itself is but a reflex process in a dynamic sense.

The conclusions of Schafer[7] are:

(1) "Every nerve cell (neuron of Waldeyer) is a structural element anatomically isolated but physiologically connected.

(2) Physiological continuity is due to ramified processes and contact of these with (a) other processes; (b) other neuron bodies.

(3) That the same nerve impulses do not necessarily pass from one element of a nerve chain to the next but that more probably new impulses, often of different rythm are generated in the successive elements of the chain."

To these I would add: Impulses do not necessarily generate functionally visible impulses, but may be transformed into "potential energy" (in storage neurons) e. g. memory, inhibition, psychic processes generally.

These conclusions involve as well as emphasize the important conception that brain efficiency (potentiality)

***[9]. "We can no longer think of nerve cells as the sources of nerve energy, as parts of a divided "nerve battery" whence nerve fibres conduct the force produced. They are the vital elements in the machine, but they have nothing to do with its dynamics. Into the protoplasm of the cell pass the fibrils which conduct nerve energy; through it they course unbroken; from it they pass, contiguous, as the elements of the axis-cylinder of a nerve fibre."—Gowers: Dynamics of Life, p. 47.**

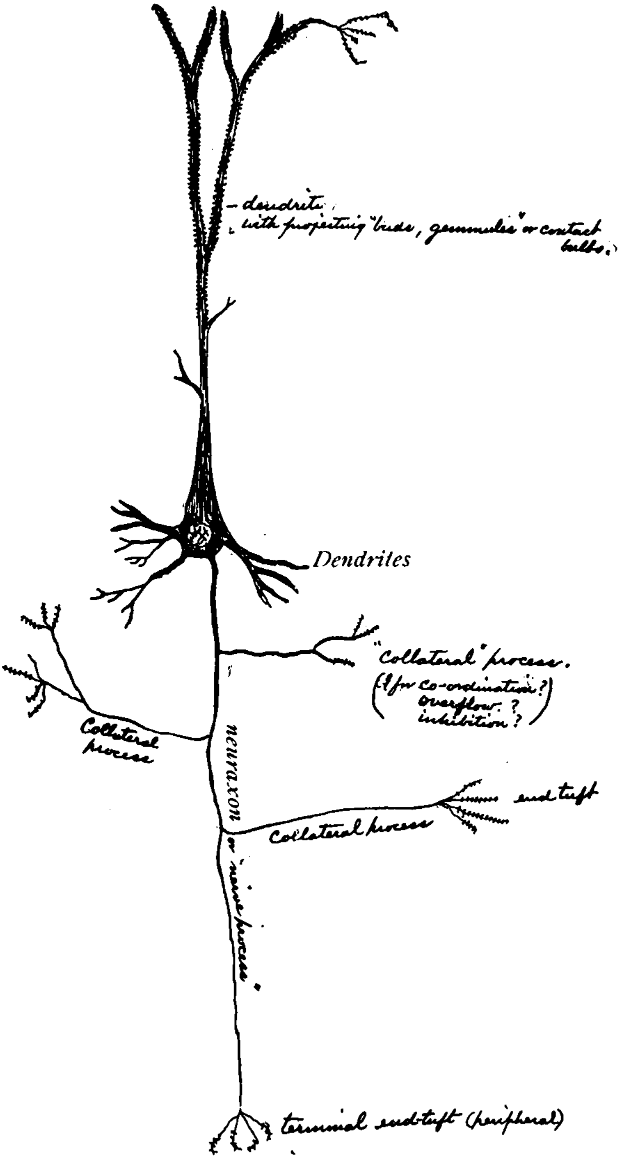

FIG. 1.—The Neuron of Waldeyer. A pyramidal neuron of the motor cortex. (Modified from Schafer.)

depends directly on the number and complexity of neuron ramifications and on the completeness of their inter-relations by means of which are brought about the varied and complex activities of which the nervous system is capable. Mere size or weight of mass is of minor importance.

PATHOLOGICAL CONSIDERATIONS.

The various hypotheses which have been advanced to account for the location and nature of the Epileptic convulsion, e. g. the theories of "special convulsive centres" (Brown-Séquard, Schiff, Nothnagel); of "epileptogenous peripheral zones" (Brown-Séquard and others); of "induration of the cornu-ammonis" (Meynert, Sommer, Bourneville and others); of anæmia and hyperæmia, hypertrophy and atrophy of the cerebral convolutions have finally given way one by one to the conclusions, almost universal at the present day, that (1) the actual origin of the epileptic convulsion is in the cortex cerebri [16]; and (2) that its nature is an "explosive discharge" in "unstable nerve tissue."

The remarkable chemical complexity of nerve tissue, composed as it is of some three hundred or more different elements and compounds has been invoked by Gowers[9] and others, as a possible or probable explanation of the epileptic "explosion." While this deserves great weight in any consideration of the subject, yet it seems hardly necessary to consider it the sole or even chief cause, until the possible anatomical and physiological factors have first been exhausted.

So long as the so-called nerve-cell (now neuron-body) was considered the ultimate beginning or destination of the axis-cylinder constituents, the alpha and omega of nervous activity, it was quite natural to seek within it for the actual cause of epilepsy and other convulsive phenomena; and we have consequently the prevailing views of their ultimate pathology as an "explosive discharge" in "unstable nerve cells of the cortex cerebri." It is difficult to see why a tissue confessedly imperfect in chemical structure, and presumably weakened in vitality, should be accused of acting with such undue violence.

The researches quoted in preceding pages, however, carry the ultimate fibrillæ composing the axis-cylinder *through* the neuron-body, to finally ramify in various "neuro-plexuses," composed of multitudinous interlac-

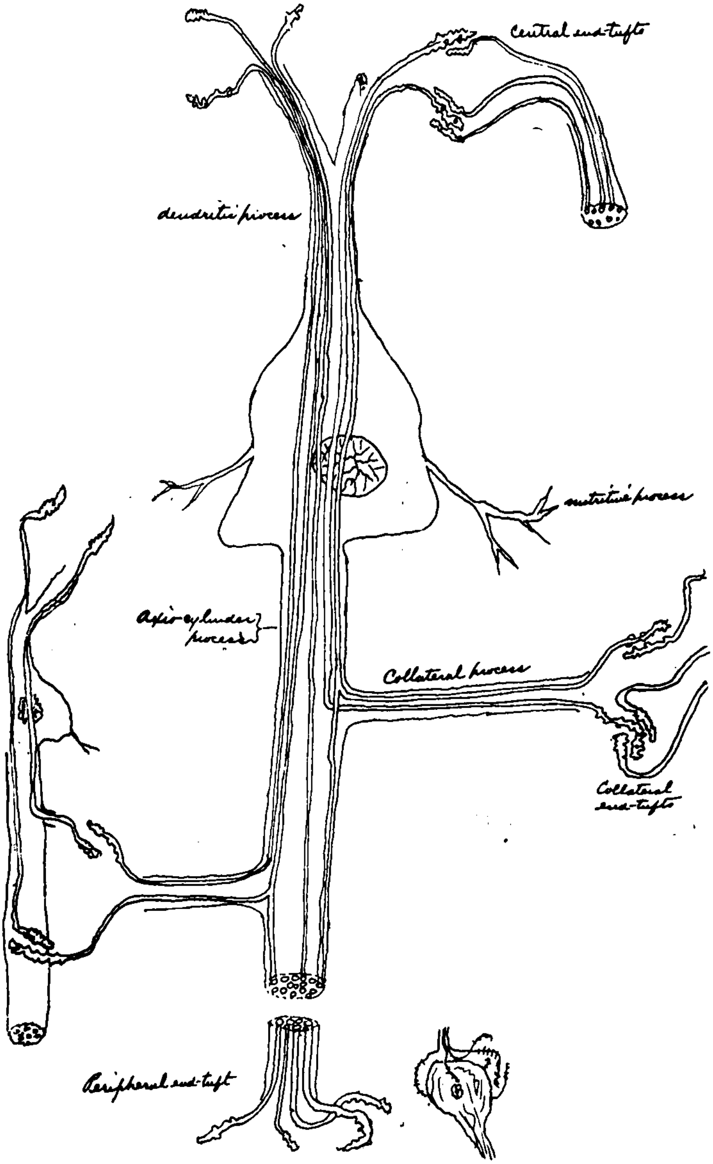

FIG. 2.—Hypothetical Neuron with bifurcating tubular fibrillæ. (After Schultze and Schafer (modified.)

ing "end-tufts" with their contact buds or gemmules which occupy the regions formerly included under the comprehensive term "the spongy gray matter;" a very poor name in the light of our present knowledge, since it applies an irregularity of structure and of relations which is quite at variance with the complexity and nicety of function we know it to possess.

In this microscopic jungle in which each individual twig and bud are essential to the perfection of the whole, we must seek, in the opinion of the writer, for the ultimate demonstrable lesions of epilepsy and other convulsive disorders, including the choreas, the hysterias and even the convulsions of toxic origin such as uræmia.

This brings us to the subject of the functional nature of cortical activity in general, and its relations to epileptic and other convulsive phenomena. While for clinical purposes the present day doctrines of cerebral localization probably rest upon a firm foundation so far as they go, it is extremely probable that the most important action of the cerebral cortex may be summed up in one word, *inhibition*, a functional entity whose existence we cannot doubt, however little we may know of its ultimate processes. In other words, what passes current for a "centre of action" is, in most cases, a centre for preventing, checking, directing, controlling and combining various activities which might otherwise occur but in different order or intensity. The strongest confirmation of this view, perhaps, is furnished by the now famous dog of Goltz' which, deprived of its cerebral hemispheres lived for eighteen months. "This dog was able during its lifetime to employ its limbs in walking, running and standing; he perceived tactile irritation of all parts of the body, and could be awakened from a deep sleep by these excitements or loud noises. He possessed a distinct sensation of the position of his members, and could unquestionably be incited to adaptive activity by such sensory stimuli. Nor was he totally blind, though it could not be proven that he was so affected by visual sensations as to modify the position or movements of the body. It was evident that hunger and gustatory sensations remained. The animal was profoundly imbecile, and it was impossible to enter into any sort of personal relation to him. No expressions of joy or fear escaped him. In restless and unvarying round he ran in his cage. With the exception of the gradual re-acquirement of the power to feed himself he never

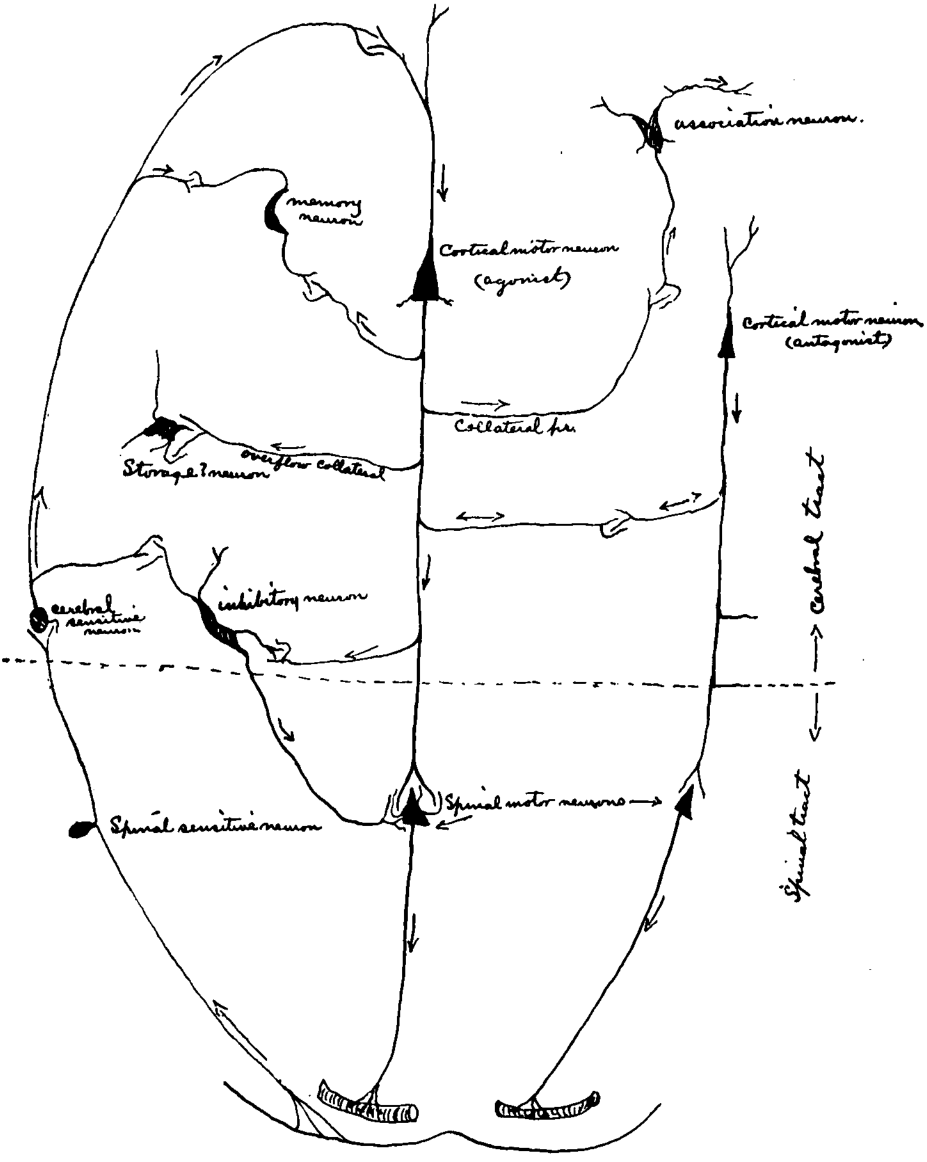

FIG. 3. Hypothetical seusori-motor arc and connections.

learned anything. Every trace of methodical activity was lost. The most remarkable deficiency resulting from the removal of the cerebrum was the suppression of all expressions which betray understanding, memory, reflection and intelligence in the animal. On the other hand those faculties remained intact which could be exercised without these functions, such as a certain degree of motor powers, sensation and general irritability."

Inhibition—the dynamic expression of a combination of functions which includes understanding, memory, reflection and intelligence is, without doubt, the highest and most important function of the cortex in a motor sense at least. Abolish this action *without destroying others*, and every passing breeze would set up in us its own convulsion, of greater or less degree; much as the passing circus actually does in the average small boy with his undeveloped inhibitory mechanisms. Any interference with so important a process can hardly fail to be attended with more or less startling effects as regards the phenomena of neuro-dynamics in general.

The only reason probably that Goltz's dog above referred to did not develop epilepsy, was that the *entire* cortex was removed, thus converting him into an automaton, not subject to the varying excitations which bring out the full activity of the cortex. On the other hand we may note that a disease which destroys the cortex piece meal so to speak, as for example, paretic dementia, is peculiarly liable to be attended with convulsive phenomena closely resembling epilepsy.

In this connection we may note also, the observations of Dercum[18] (quoted by Hare[19]), who, in autopsies on twelve cases of epilepsy, found in nearly all, evidences of "mechanical hindrance to brain development," besides other pathological changes.

Further, the great preponderance of epilepsy in early life (75 per cent. under twenty years), a period during which the demands for inhibition are increasing at a rapid rate, would of itself indicate a failure on the part of inhibitory mechanisms to keep pace in development with the activity of those which it is their office to control. As Sachs[20] states, "The removal of inhibition through disease of such (higher cortical) centres liberates the energy of the lower centres."

In the dynamic sense, therefore, all that is necessary to the production of a convulsion (*i.e.*, an unregulated motor discharge) is an incoming "sensory" impulse, ex-

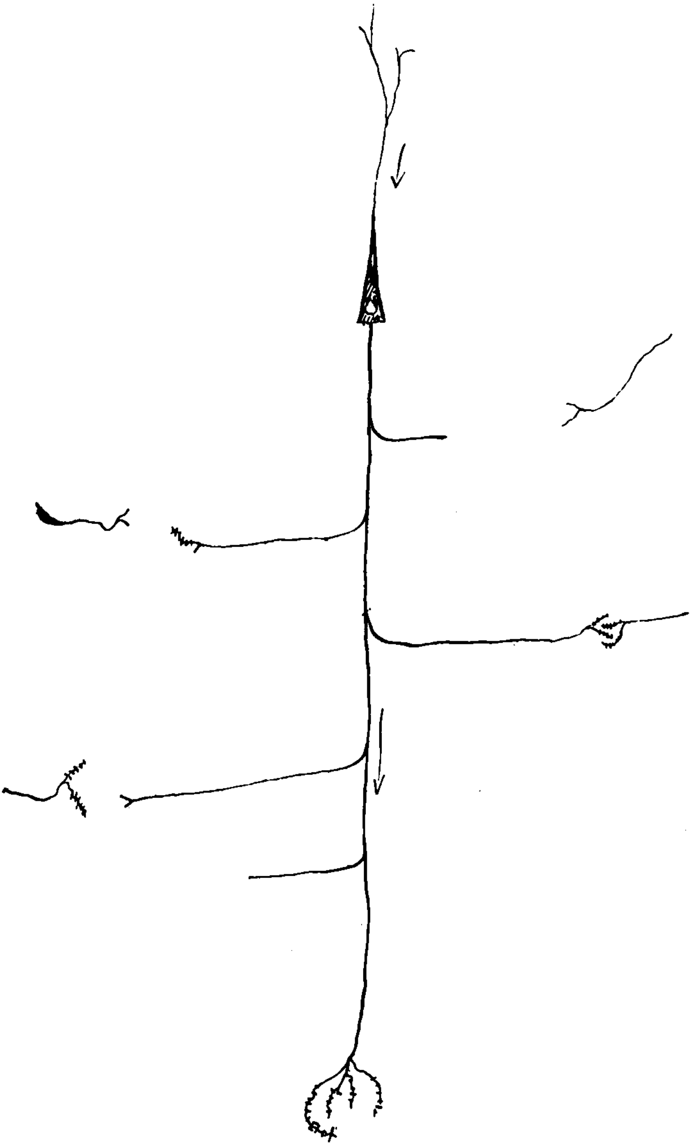

FIG. 4.—Pyramidal motor Neuron with incomplete collaterals impairing inhibition, association, motor memories, storage, etc., and by safety provision for overflow — increasing the outgoing "tension" or "pressure" in the axis-cylinder. (Diagrammatic.)

citing an out-going "motor" discharge, which discharge is not inhibited. In other words *cannot avail itself of* a proper number of "shunting," regulating or distributing mechanisms. The discharge being thus unrestrained by the proper inhibitory action, the phenomena of exhaustion naturally follow.

Our attention is naturally directed at this point to the "great pyramidal" neurons of the motor area of the cortex, generally conceded to be the mechanisms most directly concerned in the initiation of voluntary movements. What are their connections—known or inferred? and what bearing may they have on convulsive phenomena generally?

A hypothetical scheme of mechanisms (necessarily neurons or parts of neurons), probably required to produce the simplest motor action under normal circumstances is presented in Fig. 3.

It is quite evident that hereditary or developmental defects, trauma, toxines and degenerative processes,—in short, all the recognized causes of epilepsy, would tend to fall with especial primary severity on the *terminations* of the neuron-processes, in accordance with the pathological law that those portions of the neuron ramifications farthest from their source of nutrition (the neuron body) are the first to suffer from such causes as impair the vitality of the neuron body, or the neuron as a whole.

The collateral processes, on account of their length, delicacy and general direction, would be especially liable to damage of various degrees, the consequences of which must impair their "conducting" or functionating capacity, whatever that may be. Further, it would seem, from a dynamic standpoint, that the molecular play which we commonly call the "nerve current" must be productive of a certain "stress, tension, or pressure" in the axis-cylinder along which it passes. Should this stress attain undue proportions in any neuron, one of two events would seem likely to occur, namely: 1. A distribution to other areas, through contact with other neurons, which distribution may subserve purposes of memory, inhibition, or "conservation of energy." The most feasible route by which this "shunting" might occur would appear to be the "collateral' processes. (See Fig. 3).

2. Any failure in the efficiency of this supposed "shunting" process would be attended with undue expenditure of energy on lower centres, resulting in a convulsive action of the centre so over stimulated (see Fig.

4). In the illustration here presented only the motor aspect of the subject is considered, for the sake of simplicity. It is quite evident, however, that processes *other than motor* may readily be involved, thus accounting for the varying "types" of epilepsy, sensory, motor, psychic, which probably depend on the region damaged and the functions of the mechanisms there situated. That the defects referred to should preponderate in the collaterals of the great pyramidal projection tracts—is rendered probable by the fact that these are the last to reach full development (myelinate). And it seems quite conceivable that defects in myelination of collaterals would have in many cases the same influence as deficiency of collaterals themselves.

The well-known hereditary inter-relations of chorea with epilepsy, also suggest an homology in causation, viz: that the lesion in chorea is of a simlar nature, but less widespread, perhaps oftener a mere retarded development in collateral arborizations, rather than an absence or destruction. This view also accounts for the curability by time and hygiene (often without drugs) of most cases of juvenile chorea, and for the incurability of those cases developing in adult life, where the defect is more likely degenerative in nature.

In both diseases the essential dynamical defect is a lack of *inhibition*, a process pre-eminently characteristic of the cortex and almost necessarily dependent on a widespread inter-communication of the neuron processes.

The "spread of the discharge from centre to centre" and the "tendency to recurrence" of the paroxysms, have been much commented on as peculiarities of epilepsy.

The former is readily accounted for on the foregoing basis, when it is remembered that defect in collaterals means also defect in their myelin sheaths, the insulating material, so to speak, of the neuron. As for the latter, an increasing deterioration of collaterals already affected with the consequent involvment of others would seem to be a sufficient explanation.

An objection that may be raised to the views here presented, is the therapeutic one, that remedies often lessen the frequency or severity of the attacks. But what are these remedies, and what their physiological action? Simply and solely drugs that lessen the incoming sensory excitation. The bromides of the alkalies, the vegetable depressants, the coal tar anæsthetics, etc.

Did any one ever know them to absolutely cure a well-defined case of prolonged duration? On the other hand-cases occur of undoubted epilepsy which recover permanently under careful hygienic and nutrient treatment, and to whom some drug or other may have been administered. These cases, if sifted, will be found mostly, perhaps always, in the early developmental period of life and this would suggest that they were simply *examples of delayed development* of *collateral or other processes*, which has been finally completed through the hygienic measures adopted and *time*.

As may readily be seen by all familiar with the technique of neuro-pathological investigation, even with the latest additions to our resources, the difficulties in the way of an actual demonstration of these supposed defects in collateral processes and end-brushes are enormous, yet we cannot say insurmountable; for who can set a limit to human achievement in this direction after the advances of the past ten years? May we not hope that the obstacles, great though they seem, may yet yield to the persistent, painstaking efforts of future investigators, as apparently equally difficult problems have yielded in the past.

GENERAL SUMMARY.

The foregoing considerations, anatomical, physiological and pathological, would appear to the writer to justify the following propositions as a working hypothesis:

(1) That epilepsy, the choreas and probably most convulsive disorders, are the dynamical expression of an *inhibitory insufficiency;* not indications of an over production of nerve energy, nor "explosions" due to a "molecular instability," *per se*.

(2) That the cause of this inhibitory insufficiency is to be sought for in the end-brushes of collateral processes of various cortical neurons, the situation varying with the "type" of the disease, whether sensory, psychic or motor.

(3) That the defect consists most probably, in a *structural incompleteness* (small capacity, defective insulation imperfect contact), or a *numerical deficiency*, or both, in the collateral processes of the neurons referred to.

(4) Defective collaterals may favor occurrence of convulsions in two ways: (a) by impairing connection with other neurons (inhibitory, storage?); (b) by increased

"resistance" to overflow currents, causing temporary over-charging of motor axis-cylinders.

The above conception of the anatomico-dynamic basis of convulsive phenomena I would call the "collateral theory."

From the point of view here taken it is quite obvious that cases of epilepsy would naturally be arranged under three heads, each of which would present important differences as regards prognosis and treatment.

(1) *Primary* or *developmental* type, comprising the "idiopathic" cases under twenty years of age. In these, the younger the subject and the better the heredity and environment, the better the prognosis under intelligent treatment. Ultimate result depending on the possibility of promoting further and equable development of "collateral" communications with inhibitory mechanisms.

(2) The *accidental* forms: Those due to trauma, syphilis, lead, toxines, etc. The prognosis here varying with the longer or shorter duration, and the possibility of removal of the cause; being always favorable so long as permanent structural changes in collaterals and inhibitory mechanisms have not occurred.

(3) The *degenerative* type: The rare cases of adult life and old age (not "accidental") belong in this category.

Here palliation only is to be expected, as in degenerative changes elsewhere. In all forms the rational indications for treatment are: To lessen the incoming sensory excitation by diet, hygiene, occupation, medicines, and so diminish the intensity of motor responses or other "discharges," which are not provided with suitable "overflow" and "inhibitory mechanisms."

In short, to take off pressure, favor nutrition and educate those elements which remain undamaged.

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